Women and Ischemia Syndrome Evaluation (WISE)
Diagnosis and Pathophysiology of Ischemic Heart Disease
Workshop

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Session II

1. Topic and Author

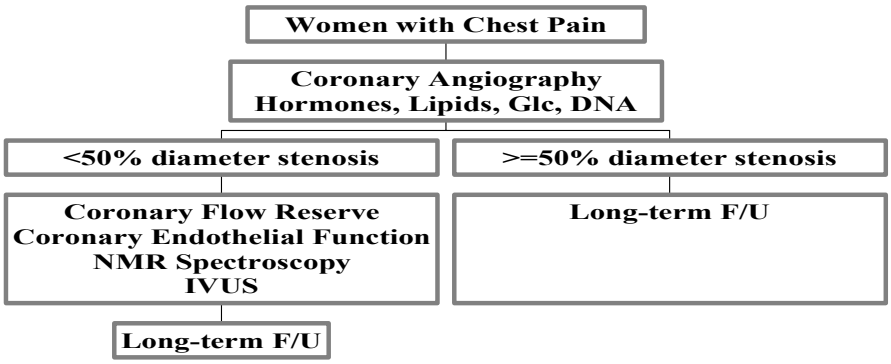
Coronary Microvascular Disease in Women
Steven E. Reis, MD

2. Where we stand in 2002. Overview/rationale for inclusion of topic.

Chest pain typical for angina pectoris is less likely to be associated with obstructive epicardial coronary artery disease (CAD) in women than men [1]. Although women with chest pain in the absence of CAD are at low risk for adverse cardiac events, they are frequently limited by debilitating symptoms which may prompt repeated diagnostic evaluations and hospitalizations. These women are commonly diagnosed with "Syndrome X," defined as chest pain, an ischemic stress test response and angiographically normal coronary arteries [2]. "Syndrome X" likely results from coronary microvascular dysfunction, which is a disordered function of the smaller coronary resistance vessels.

Scope of Problem

Women who undergo cardiac catheterization to evaluate chest pain frequently have no angiographic evidence of obstructive coronary artery disease (CAD). Most of these women do not undergo further invasive testing to determine whether their chest pain is related to abnormal coronary physiology (i.e., coronary microvascular dysfunction or epicardial coronary vasospasm). As part of the WISE study [3], a subgroup of women with chest pain in the absence of obstructive CAD underwent invasive assessment of their coronary artery physiology:



Assessment of coronary flow reserve and endothelial function by measurement of changes in coronary flow in response to adenosine and mental stress, respectively, demonstrated that microvascular dysfunction and coronary vasospasm were present in 52% and 4%, respectively, of women with chest pain in the absence of obstructive CAD.

Implications

Although chest pain in women with coronary microvascular dysfunction may be related to increased visceral sensitivity or low pain threshold, recent studies have suggested that these women may have an increased risk of

inducible myocardial ischemia and subendocardial hypoperfusion. In WISE, Buchthal et al. used P-31 NMR spectroscopy to demonstrate that 20% women with chest pain in the absence of CAD had significant inducible myocardial ischemia [4]. These women had decreases in the phosphocreatine:ATP ratio during handgrip exercise that were more than 2 standard deviations below the mean value of control women without chest pain. Panting and colleagues used magnetic resonance imaging to demonstrate that Syndrome X is associated with subendocardial hypoperfusion and chest pain induced by intravenous adenosine [5]. Specifically, In 20 patients with syndrome X, the ratio of subendocardial to subepicardial myocardial perfusion reserve index was significantly lower than that of 10 control subjects (0.61±0.11 vs. 0.85±0.13, P=.002). These two studies are consistent with the hypothesis that a subgroup of women with chest pain in the absence of obstructive CAD may have microvascular dysfunction associated with stress-induced subendocardial hypoperfusion and metabolic ischemia.

Possible Mechanisms

The pathophysiologic mechanism for coronary microvascular dysfunction is unknown. The WISE study is indirectly exploring the hypothesis that this syndrome is associated microvascular endothelial dysfunction by measuring coronary flow responses to intracoronary adenosine and acetylcholine, risk factors for endothelial dysfunction, and subclinical atherosclerosis manifested by IVUS-detected epicardial coronary artery disease. Results demonstrate that microvascular dysfunction manifested by abnormal coronary flow reserve is not associated with age, hypertension, hyperlipidemia or lipid levels, menopausal status, cigarette use, or diabetes [6]. However, women with microvascular dysfunction were significantly less likely to be using postmenopausal hormone replacement therapy (40 vs. 60%, P=.03). Although other WISE studies are ongoing, preliminary analyses suggest that women with chest pain in the absence of obstructive CAD may have significant epicardial coronary atherosclerosis detected by intracoronary IVUS (personal communication, Carl J. Pepine, MD). However, the relationship between microvascular dysfunction and microvascular atherosclerosis is uncertain.

Atherosclerosis is a chronic "inflammatory-fibroproliferative" disease of the arterial wall that is modulated by the immune system. Therefore, microvascular atherosclerosis may be related to systemic inflammation. Alternatively, inflammation of the coronary microvasculature may result in abnormal physiology resulting in microvascular dysfunction. The WISE study investigated the association between inflammation and coronary microvascular dysfunction by correlating levels of inflammatory markers with coronary microvascular physiology in women with chest pain in the absence of obstructive CAD. We found that CFR did not correlate with levels of the inflammatory markers hsCRP (r_s=-0.07, P=0.53), IL-6 (r_s=-0.12, P=0.31), IL-18 (r_s=0.14, P=0.23), TNF-α (r_s=-0.09, P=0.43), and TGF-β1 (r_s=0.02, P=0.84). Furthermore, when analyzing microvascular function in women as abnormal versus normal, the median levels of inflammatory markers were similar between the two groups (hsCRP: 0.32 vs. 0.25 mg/dl, P=0.80; IL-6: 2.89 vs. 2.39 pg/ml, P=0.63; IL-18: 218 vs. 227 pg/ml, P=0.59; TNFα: 2.7 vs. 2.4 pg/ml, P=0.43; TGF-β1: 9928 vs. 12436 pg/ml, P=0.76, in abnormal vs. normal microvascular function, respectively). These results suggest that inflammation does not play a pathophysiologic role in coronary microvascular dysfunction in women.

Summary

Coronary microvascular dysfunction is prevalent in women with chest pain in the absence of obstructive CAD. Although their long-term prognosis is uncertain, these women are at increased risk of having inducible subendocardial hypoperfusion. Inducible metabolic ischemia is also prevalent in women with chest pain not attributable to CAD. The pathophysiologic mechanism of coronary microvascular dysfunction is not certain, although it does not appear to be related to atherosclerosis risk factors or inflammation. Further studies are need to identify the prognosis and mechanism of microvascular dysfunction in women with chest pain.

3. Current challenges and the most important issues for future research

Women with chest pain and coronary microvascular dysfunction need to be evaluated to study:

1. Long-term prognosis

2. Prevalence of inducible myocardial ischemia detected by P-31 NMR spectroscopy
3. Roles of coronary microvascular atherosclerosis and arterial myocyte dysfunction in the pathophysiologic mechanism of microvascular dysfunction
4. Noninvasive methodologies to evaluate coronary microvascular physiology
5. Pathophysiologic-guided treatment

4. Current challenges in the areas of communicating messages to health care community, patients and the public

Women with chest pain in the absence of obstructive CAD are frequently informed that they have a noncardiac etiology of their symptoms. Health care providers, patients, and the public need to understand the prevalence, clinical presentation, diagnostic evaluation, and treatment for coronary microvascular dysfunction.

5. Translating new findings to improved diagnosis and treatment/saving lives.

Recent studies of the implications of coronary microvascular dysfunction can be used to improve the diagnosis and treatment of women with chest pain. First, clinicians should consider invasive measurement of coronary flow reserve in women with chest pain who do not have obstructive CAD diagnosed during coronary angiography. Second, the results of clinical trials that have evaluated treatment of patients with chest pain in the absence of CAD (e.g., L-arginine, estrogen) should be considered when evaluating women with this presentation.

6. References.

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6. Reis SE, Holubkov R, Smith AJC, et al. Coronary microvascular dysfunction is highly prevalent in women with chest pain in the absence of coronary artery disease: Results from the NHLBI WISE Study. Am Heart J 2001;141:735-41.